General

Guideline Title

ACR Appropriateness Criteria® anal cancer.

Bibliographic Source(s)

Hong TS, Pretz JL, Suh WW, Herman JM, Abdel-Wahab M, Azad N, Blackstock AW, Das P, Goodman KA, Jabbour SK, Jones WE III, Konski AA, Koong AC, Rodriguez-Bigas M, Small W Jr, Thomas CR Jr, Zook J, Expert Panel on Radiation Oncologyâ€“Rectal/Anal Cancer. ACR Appropriateness CriteriaÂ® anal cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2013. 14 p. [56 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Poggi MM, Konski AA, Suh WW, Blackstock AW, Herman JM, Hong TS, Rodriguez-Bigas M, Small W Jr, Thomas CR Jr, Venook AP, Zook J, Expert Panel on Radiation Oncology-Rectal/Anal Cancer. ACR Appropriateness Criteria® anal cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2010. 11 p.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Anal Cancer

Variant 1: 45-year-old patient, T3N0M0. Karnofsky performance score (KPS) 80.

Treatment	Rating	Comments
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	2	
RT + 5-FU	2	
External beam + brachytherapy	2	
APR	1	
If RT + Chemotherapy: RT Dose to Primary		
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
45 Gy/1.8 Gy	3	
50.4 Gy/1.8 Gy	5	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	8	
Technique: RT		
IMRT	8	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	8	
Pelvis + primary + lateral inguinal LNs	7	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 50-year-old patient, T1N2M0 right inguinal 2-cm node + M0. KPS 90.

Treatment	Rating	Comments
Pre-RT Induction Chemotherapy		
5-FU + MMC	1	
5-FU + CDDP	1	
Primary Treatment		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	2	
APR	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Dose to Primary + Right Inguinal Node with RT + Chemotherapy	Rating	Comments
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	3	
50.4 Gy/1.8 Gy	7	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	6	
Technique: RT		
IMRT	8	
AP/PA photons	6	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	5	
If RT + Chemotherapy: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	2	
Pelvis + primary + lateral inguinal LNs	9	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 73-year-old patient, T1N0M0. KPS 80.

Treatment	Rating	Comments
Local Excision, Negative Margins		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	4	
APR	1	
Brachytherapy alone	1	
Local Excision, Positive Margins		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	4	
APR	1	
Brachytherapy alone	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
RT alone	4	
Re-excision	1	
APR	1	
If RT + Chemotherapy: RT Dose to Primary		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	7	
50.4 Gy/1.8 Gy	7	
54 Gy/1.8 Gy	5	
59.4 Gy/1.8 Gy	2	
Technique: RT		
IMRT	7	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	8	
Pelvis + primary + lateral inguinal LNs	4	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 65-year-old patient, T2N0M0. KPS 80.

Treatment	Rating	Comments
RT + 5-FU + MMC	9	For CDDP, see text.
RT + 5-FU	6	
RT alone	4	
External beam + brachytherapy	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
If RT + Chemotherapy: RT Dose to Primary		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	4	
50.4 Gy/1.8 Gy	8	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	3	
Technique: RT		
IMRT	8	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	8	
Pelvis + primary + lateral inguinal LNs	6	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 45-year-old patient, T4N3M0. KPS 80.

Treatment	Rating	Comments
Pre-RT Induction Chemotherapy		
5-FU + MMC	1	
5-FU + CDDP	1	
Primary Treatment		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
APR + node dissection	1	
APR + node dissection + chemoradiation	1	
RT + Chemotherapy: RT Dose to Primary		
50.4 Gy/1.8 Gy	2	
54 Gy/1.8 Gy	7	
55.8 Gy/1.8 Gy	7	
59.4 Gy/1.8 Gy	8	
70.2 Gy/1.8 Gy	3	
Technique: RT		
IMRT	8	
AP/PA photons	6	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	2	
Pelvis + primary + lateral inguinal LNs	9	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: 56-year-old patient, T3N0M0, 50.4 Gy dose with 5-FU + MMC with initial complete response, now with biopsy of primary at 7 months = positive (recurrent).

Treatment	Rating	Comments
APR	9	
Postoperative chemotherapy + APR	3	
Additional RT + chemotherapy	2	
Brachytherapy alone	1	
Local excision	1	

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		
Treatment	Rating	Comments

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Background

Anal canal cancers are rare, accounting for approximately 10% of cancers in the anorectal region and approximately 6,230 cases annually in the United States. Beginning in the early 1980s, the traditional management of abdominoperineal resection (APR) for tumors of the anal region was progressively replaced by radiotherapy alone and, eventually, by chemoradiation. The emergence of a successful nonsurgical treatment for anal cancer was a paradigm shift and helped usher in a new era of organ-preserving treatment for other cancer disease sites. Although there are no randomized trials comparing APR with radiation or chemoradiation, chemoradiation has supplanted other forms of therapy primarily because of its superior local control and colostomy-free survival rates for most patients with anal cancer. APR (and radiotherapy to a lesser degree) results in a permanent colostomy with its associated functional, anatomic, and psychological complications. The treatment of anal cancer with chemoradiation has served as a prototype for organ-preserving treatment attempts of esophageal and other cancers.

Histology

Tumors of the anal region are most frequently keratinizing or nonkeratinizing squamous cell carcinoma. Basaloid cancers arise from the functional zone just above the dentate line and are considered by most investigators to be types of squamous cancer. These and other subtypes of squamous cell carcinoma are treated like squamous cell carcinomas, as there is no prognostic significance. Primary adenocarcinoma of the anus is rare; it is an aggressive disease that is associated with a high rate of distant metastases.

The role of routine chemoradiation for adenocarcinoma is not firmly demonstrated in the literature. A report from the MD Anderson Cancer Center recommended preoperative chemoradiation followed by surgery. However, in a Rare Cancer Network retrospective multicenter study reporting on a group of 82 patients, outcomes did not greatly differ from results reported with squamous cell cancer of the anus. Small-cell carcinoma of the anal region is even rarer, and experience in treating it is limited. Other rare histologies include melanoma, lymphoma (including mucosa-associated lymphoid tissue lymphomas), and sarcoma.

Because squamous histology is by far the most common, it should be noted that the evidence cited in this review is primarily applicable to squamous cell carcinoma of the anal canal; treatment of other histologies is not as well defined in the literature.

Distant Metastases

Systemic spread of squamous cell anal cancer occurs in less than 10% of cases. The liver and lungs are the most common sites of distant spread. Treatment of such metastases in patients is varied. The risk for distant metastases in adenocarcinoma of the anus is 28% higher.

Tumors of the Anal Margin

The anal margin is defined generally as a 5-cm radius outside but not impinging upon the anal verge. Due to tumor location and consequent proclivity for early diagnosis, patients with these tumors tend to have a better prognosis. Patients with very early stage (T1N0M0) anal margin cancer are very well managed by local wide excision or by radiotherapy alone, similar to treatment for a skin cancer. The recommended radiation dose in these cases is between 60 and 65 Gy in 6 to 7 weeks. More advanced diseases at the anal margin or lesions that involve the anal verge are managed stage-for-stage with treatment options similar to those for anal canal cancers.

Staging

Several clinical staging systems have been proposed and used in the past, including classifications from the Mayo Clinic, Roswell Park, and the Centre Léon Bérard. The TNM classification system has been used in the treatment guidelines because it is suitable for a disease treated primarily with nonsurgical means and because of its increasing acceptance in the literature.

Because anal cancer is now typically treated nonsurgically, optimal treatment and outcomes are dependent on adequate pretreatment staging. The combination of positron emission tomography (PET) and/or computed tomography (CT) for identifying the primary tumor and involved nodes should be used. These modalities, although quite good, are not perfect, and pathologic staging with a sentinel lymph node biopsy may be considered.

Prevention

Anal cancer is preceded by high-grade anal intraepithelial neoplasia (AIN). AIN can be caused by infection with human papillomavirus (HPV),

primarily types 16 and 18. The quadrivalent HPV vaccine, when given prior to HPV exposure, has been shown to reduce the rates of AIN and should be considered in populations at high risk for anal cancer, which includes men who have sex with men, women with cervical or vulvar cancer, or individuals who are immunosuppressed.

Prognostic Factors

The size of the primary tumor and the presence of nodal or distant metastases are determinates of outcome. Patients with de novo tumors >5 cm are at significantly increased risk of requiring a colostomy, and such tumors contribute to inferior disease-free and overall survival rates. Additionally, male gender and positive human immunodeficiency virus (HIV) status may portend unfavorable long-term outcomes.

Treatments

Surgical Management

Radical surgery in the form of APR that resulted in permanent colostomies was the standard treatment of choice for anal cancers until the 1970s, before radiotherapy alone. Then, chemoradiation supplanted APR. APR yielded 5-year survival rates of approximately 50% and local recurrence rates of approximately 30%. The role of APR for chemoradiation failures is discussed under "Salvage Treatment," below.

Local excision with wide margins may be an alternative to radiotherapy in the treatment of selected patients with T1N0M0 anal canal cancers as long as sphincter function can be preserved. The cure rates are markedly lower, however: approximately 60% at 5 years, with local recurrences at approximately 40%. Reciprocal figures for radiotherapy alone note a 5-year survival rate of 90% to 100% and a local failure rate of 10% to 20%. Local excision alone should be reserved for special clinical circumstances such as a patient with a poor performance status and/or significant comorbidities. (See the National Guideline Clearinghouse [NGC] summary ACR Appropriateness Criteria® local excision in early-stage rectal cancer, although note that some of the presented data refers to excision of adenocarcinoma, a relatively rare histology in the anal canal.)

Biopsies for initial diagnosis and for establishing local residual or recurrent disease should also be done with caution in the interest of sphincter function.

Radiation Alone—External Beam

The efficacy of radiation alone in patients with anal cancer has been well studied. One study reported on 270 patients with T1-T4 carcinoma of the anal canal treated with radiation alone. Local control for tumors <4 cm was 90% at 10 years, whereas it was 65% at 10 years for tumors >4 cm. Overall, 57% of patients maintained normal anal function. Authors of another study reported similar results with radiation alone in a study for which local control was related to T stage. The authors reported 100% local control for T1 tumors, 86% for T2, 92% for T3, and 63% for T4. Overall, 74% of patients maintained a functional anus. Despite encouraging results of radiation alone, chemoradiation has been shown to be superior to radiation in patients with anal canal cancer.

Radiation Alone—Interstitial Radiation (Brachytherapy)

Few studies have reported on the efficacy of brachytherapy alone. One study reported that brachytherapy was relatively effective for patients with small node-negative anal canal cancer. Local control for tumors <5 cm was 64% and diminished to 23% for tumors >5 cm. Survival was also related to tumor size. The long-term survival rate was 60% for tumors <5 cm and only 30% for tumors >5 cm. Eighty-two percent of patients who had no evidence of recurrent cancer retained normal anal function. No direct comparison of brachytherapy to chemoradiation has been made; however, these results are clearly inferior to those of combined-modality treatment.

Radiation Alone Versus Chemoradiation

Concurrent chemotherapy and radiation yield results superior to those of radiation alone or radical surgical resection. Consequently, chemoradiation is now the standard of care. Authors of one study reported the results of one of the largest experiences with chemoradiation for anal canal cancer. They described 192 patients treated with either radiation alone, radiation with 5-fluorouracil (5-FU), or radiation with 5-FU and mitomycin (MMC). Radiation treatment with concurrent 5-FU and MMC resulted in the highest degree of local control and the best 5-year survival rate (86% and 78%, respectively); however, MMC was associated with increased frequency and severity of toxicity, particularly hematological toxicity.

Two major randomized studies have compared the use of radiation alone to combined chemoradiation. Results were reported of a study by the European Organization for Research and Treatment of Cancer Radiotherapy (EORTC) that compared radiation alone to radiation plus concurrent chemotherapy for patients with T3, T4, and N0-N3 tumors and patients with T1, T2, and N1-3 tumors. In that study, local control increased from 55% with radiation alone to 73% when combined with chemoradiation. Similarly, the colostomy-free rate increased from 45% with radiation alone to 77% with combined-modality therapy. The 5-year survival rate was 56%, and there was no difference in late toxicity between the 2 arms. The

United Kingdom Coordinating Committee on Cancer Research Anal Cancer Working Party reported the results of radiation alone versus chemoradiation for patients with T1-T4, N positive/negative tumors. Its findings indicated that local control with radiation alone was inferior to that of chemoradiation, 41% versus 64%, respectively. The party concluded that chemoradiation with surgical salvage for failure was superior to radiation alone (see Variants 1 and 2, above).

Use of Mitomycin

In a large intergroup study, the use of MMC combined with 5-FU and radiation was shown to be superior to 5-FU and radiation alone. The disease-free survival rate increased from 51% with 5-FU and radiation to 73% with radiation combined with 5-FU and MMC. The colostomy rate decreased from 22% with 5-FU and radiation to 9% with radiation combined with 5-FU and MMC (see Variants 3 and 4, above).

Use of Cisplatin

Several single-institution and phase II studies have examined the use of radiation given concurrently with 5-FU and cisplatin (CDDP) rather than with 5-FU alone or 5-FU and MMC. Promising results were reported in 39 patients treated with concurrent infusional 5-FU, CDDP, and radiation. Local control was 85% at 5 years with both 5-FU and CDDP administered by infusion along with 54 to 55 Gy of radiation compared with 73% local control for patients treated with 5-FU and radiation to similar doses. Toxicities, especially hematologic toxicity, were limited. Investigators combined bolus CDDP with infusional 5-FU and radiation therapy in a phase II trial of the Eastern Cooperative Oncology Group. The regimen resulted in an overall response rate of 95%; however, significant toxicity occurred, indicating that this regimen was near the maximal tolerated dose. The difference in the toxicities in these 2 studies may be based on several variables such as the schedule of CDDP administration, the agents, or the use of induction therapy. Other investigators showed comparable overall survival, local control, and colostomy-free survival rates in 2 studies with 92 and 95 patients, respectively, with CDDP replacing MMC. Less hematologic and other toxicities may be evident with infusional CDDP, similar to the difference noted in the toxicity profile between bolus and infusional 5-FU during postoperative chemoradiation for locally advanced rectal cancer.

The EORTC published phase II data comparing MMC, continuous 5-FU, and radiation to MMC, weekly CDDP, and radiation. More patients in the CDDP arm discontinued treatment than in the 5-FU arm, and there were more grade 3 hematological toxicities with CDDP and no hematological toxicities with 5-FU. The rates of other toxicities were the same. The authors concluded, however, that since the CDDP arm had more activity it warranted further study, and the 5-FU arm did not. They also found acceptable the greater toxicity.

Most recently, a long-term update of the Radiation Therapy Oncology Group® (RTOG®) 9811 was published. This phase III trial randomized 649 patients and compared 5-FU, MMC, and radiation to induction 5-FU and CDDP followed by 5-FU, CDDP, and radiation. In the initial analysis there was a significant decrease in colostomy failures with the use of MMC, but trial researchers also reported that MMC was associated with greater grade 3-4 acute hematologic toxicity than CDDP (late toxicity was the same). At that time, with only 2.51 years of follow-up, there was no statistical difference in disease-free survival or overall survival. However, in the recent update of RTOG 9811, the use of MMC was associated with better disease-free survival (67.8% versus 57.8% at 5 years, P=.006) and better overall survival (78.3% versus 70.7% at 5 years, P=.026) when compared to the CDDP arm. There was a trend toward statistical significance in terms of locoregional relapse, colostomy-free survival, and decreased colostomy failure favoring the MMC arm.

RTOG 9811 confirmed that induction chemotherapy with CDDP and concurrent chemoradiation was inferior to upfront concurrent chemoradiation with MMC. The use of induction in the CDDP arm, however, is a potential confounder. The ACT II trial in the United Kingdom attempted to address this issue with a direct comparison of CDDP to MMC in the concurrent chemoradiation alone setting. Preliminary data with a median follow-up of 5 years presented at the 2012 American Society of Clinical Oncology meeting suggest an equivalence between radiation with 5-FU and MMC and radiation with 5-FU and CDDP. Based on the current evidence, it has been concluded that concurrent chemoradiation with 5-FU and MMC remains the standard of care.

Radiation Dose and Technique

Radiation techniques have evolved over the past decade with the advent of intensity-modulated radiation therapy (IMRT). The goal of this form of inverse planning and delivery of external beam radiotherapy is to increase the therapeutic ratio. Dosimetrically IMRT use can reduce dose to normal structures and clinically is associated with decreased acute toxicity compared to historic outcomes, with less than 25% of patients experiencing grade 3+ gastrointestinal and dermatologic toxicity. A retrospective review compared treatment of anal cancer with IMRT with conventional radiation therapy. Patients treated with conventional radiation required more treatment breaks and longer treatment duration. They reported better overall survival at 3 years, locoregional control, and progression-free survival with IMRT compared to conventional radiation (88%, 92%, and 84%, respectively for IMRT versus 52%, 57%, and 57%, respectively for conventional radiation). RTOG 0529 is a phase II study examining the ability of IMRT to reduce acute morbidity in anal cancer. Reducing acute toxicity enables patients to complete treatment with few breaks, which overall could lead to better outcomes. Since preliminary results are encouraging, the expert panel now recommends the use of IMRT as "usually appropriate" if performed outside of a protocol setting. However, it is important to note that even for patients enrolled in RTOG

0529, quality control and technical issues with IMRT were thought to be challenging, in particular with regard to target volume contouring. For T1N0 patients, high-energy photon fields that cover the pelvis in an anteroposterior (AP)/posteroanterior (PA) or 4-field box are used most often. For more advanced lesions (e.g., ≥T2 or N+), typically the pelvis and inguinal lymph nodes are treated with photons, and then electron fields are used to treat the inguinal lymph nodes to dose above the threshold of the femoral heads.

The appropriate radiation dose for anal cancer has not been fully elucidated. A minimum dose of at least 45 Gy has been established for even the earliest stage of anal cancer, T1N0. Several studies suggest that doses in excess of 55.8 Gy result in higher local control rates than lower doses. If the use of IMRT in RTOG 0529 yields expected tumor control rates while minimizing toxicity, it would provide a way to safely explore dose escalation. However, increased radiation dose did not increase local control when given in a split-course fashion in a phase II RTOG study, and currently a maximum dose of 59 Gy is standard for even the most advanced cases. A split course resulted in less grade 3 or higher toxicity; however, the colostomy rate was also higher. Therefore, a preplanned split-course of radiation is not recommended. If there are significant skin breakdown issues, a treatment break of no more than 10 days is currently allowed by the most recent RTOG protocol. Conventionally, doses of radiation between 50.4 Gy and 59.4 Gy are appropriate.

Nodal Metastasis

Anal cancers spread to the perirectal, inguinal, and internal and external iliac groups of lymph nodes. This occurs in approximately 30% of patients in surgical series. Consequently, all 4 groups of lymph nodes are included in radiotherapy fields described in chemoradiation series (see Variant 5, above).

The presence of synchronous lymph nodes in anal cancer has a marked negative influence on survival and colostomy rates. With radiotherapy alone, approximately 70% of inguinal nodes are controlled, whereas 90% of synchronous inguinal nodes are controlled with chemoradiation.

Suitability for Definitive Treatment

Most patients with anal cancer, even locally advanced disease, have good or acceptable general performance status (≥50%). Poor performance status may preclude adherence to a standard course of chemoradiation. Known HIV infection is not necessarily a contraindication to standard recommended treatments, and these patients should continue on antiretroviral therapy throughout chemoradiation. However, patients with cytopenias or with frank manifestations of acquired immunodeficiency syndrome may have a decreased ability to tolerate treatment. A patient's overall performance status, complete blood count, and T cell counts (CD3/CD4 status) should be considered in selecting therapy. Ideally, the viral load should be below 10,000, and the CD4 count should be above 200. Modern HIV therapies have made the treatment of anal cancer with standard chemoradiation much more feasible, although cases should be individualized pending large randomized trials results. Other relative reasons that might preclude definitive treatment include previous pelvic radiotherapy or surgery and underlying medical, psychiatric, and/or social reasons.

Salvage Treatment

The committee determined by consensus that progressive or recurrent disease after chemoradiation requires APR for salvage. With a median follow-up of 29 months after radical salvage surgery, authors of one study reported that the overall actuarial survival rate was 64% in 31 patients with either persistent or recurrent squamous cell cancer of the anal canal. Other investigators have shown that the use of 9 Gy along with 5-FU and CDDP can result in an approximate 50% salvage rate for patients with biopsy-proven evidence of residual malignancy 4 to 6 weeks following completion of chemoradiation; however, others argue that a complete response would be achieved with further follow-up, therefore they do not recommend a biopsy or salvage chemoradiation (see Variant 6, above).

Treatment of Adenocarcinoma

The RCN study concluded that combined treatment with chemotherapy and radiotherapy is the treatment of choice, which produces the best survival rates, and that APR should be reserved for salvage treatment of persistent or recurrent disease.

Summary

- Chemoradiation with 5-FU and MMC remains the standard of care.
- Doses of radiation between 50.4 and 59.4 Gy are most commonly used.
- The use of IMRT and CDDP is still undergoing study.
- Routine biopsy after chemoradiation is discouraged, and abdominal-perineal resection is reserved for salvage in most cases.

Abbreviations

- 5-FU, 5-fluorouracil

- AP, anteroposterior
- APR, abdominoperineal resection
- CDDP, cisplatin
- IMRT, intensity-modulated radiation therapy
- KPS, Karnofsky performance score
- LN, lymph node
- MMC, mitomycin
- PA, posteroanterior
- RT, radiation therapy

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Anal cancer

Guideline Category

Management

Treatment

Clinical Specialty

Colon and Rectal Surgery

Gastroenterology

Oncology

Radiation Oncology

Radiology

Surgery

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of therapeutic procedures for anal cancer

Target Population

Patients with anal cancer

Interventions and Practices Considered

1. Surgery
    - Local excision: negative and positive margins
    - Abdominoperineal resection (APR)
    - Groin dissection
2. Radiation therapy (RT)
    - External beam RT + brachytherapy
    - Intensity-modulated radiation therapy (IMRT)
    - Interstitial (brachytherapy)
    - Anteroposterior/posteroanterior (AP/PA) photons
    - PA + laterals + electron boost to inguinal lymph nodes
    - 4-field box
    - Consideration of RT dose to primary
    - Consideration of RT volume needed (pelvis, primary, medial and inguinal lymph nodes)
3. Chemotherapy
    - Mitomycin
    - Cisplatin
    - 5-fluorouracil
4. Combination therapy: RT and chemotherapy
5. Routine post-treatment biopsy

Major Outcomes Considered

- 5-year survival
- Local recurrence rate
- Nodal metastasis rate
- Colostomy-free survival rate

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Procedure

Staff will search in PubMed only for peer reviewed medical literature for routine searches. Any article or guideline may be used by the author in the narrative but those materials may have been identified outside of the routine literature search process.

The Medline literature search is based on keywords provided by the topic author. The two general classes of keywords are those related to the condition (e.g., ankle pain, fever) and those that describe the diagnostic or therapeutic intervention of interest (e.g., mammography, MRI).

The search terms and parameters are manipulated to produce the most relevant, current evidence to address the American College of Radiology Appropriateness Criteria (ACR AC) topic being reviewed or developed. Combining the clinical conditions and diagnostic modalities or therapeutic procedures narrows the search to be relevant to the topic. Exploding the term "diagnostic imaging" captures relevant results for diagnostic topics.

The following criteria/limits are used in the searches.

1. Articles that have abstracts available and are concerned with humans.
2. Restrict the search to the year prior to the last topic update or in some cases the author of the topic may specify which year range to use in the search. For new topics, the year range is restricted to the last 10 years unless the topic author provides other instructions.
3. May restrict the search to Adults only or Pediatrics only.
4. Articles consisting of only summaries or case reports are often excluded from final results.

The search strategy may be revised to improve the output as needed.

Number of Source Documents

The total number of source documents identified as the result of the literature search is not known.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Strength of Evidence Key

Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.

Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.

Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.

Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author drafts or revises the narrative text summarizing the evidence found in the literature. American College of Radiology (ACR) staff draft an evidence table based on the analysis of the selected literature. These tables rate the strength of the evidence (study quality) for each article included in the narrative text.

The expert panel reviews the narrative text, evidence table, and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the table. Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The appropriateness ratings for each of the procedures included in the Appropriateness Criteria topics are determined using a modified Delphi methodology. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. American College of Radiology (ACR) staff distribute surveys to the panelists along with the evidence table and narrative. Each panelist interprets the available evidence and rates each procedure. The surveys are completed by panelists without consulting other panelists. The appropriateness rating scale is an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate"; 4, 5, or 6 are in the category "may be appropriate"; and 7, 8, or 9 are in the category "usually appropriate." Each panel member assigns one rating for each procedure for a clinical scenario. The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating.

If consensus is reached, the median rating is assigned as the panel's final recommendation/rating. Consensus is defined as eighty percent (80%) agreement within a rating category. A maximum of three rounds may be conducted to reach consensus. Consensus among the panel members must be achieved to determine the final rating for each procedure.

If consensus is not reached, the panel is convened by conference call. The strengths and weaknesses of each imaging procedure that has not reached consensus are discussed and a final rating is proposed. If the panelists on the call agree, the rating is proposed as the panel's consensus. The document is circulated to all the panelists to make the final determination. If consensus cannot be reached on the call or when the document is circulated, "No consensus" appears in the rating column and the reasons for this decision are added to the comment sections.

This modified Delphi method enables each panelist to express individual interpretations of the evidence and his or her expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. A more detailed explanation of the complete process can be found in additional methodology documents found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate treatment procedures for patients with anal cancer

Potential Harms

- Abdominoperineal resection (and radiotherapy to a lesser degree) results in a permanent colostomy with its associated functional, anatomic, and psychologic complications.
- Mitomycin has been associated with increased frequency and severity of toxicity, particularly hematologic toxicity.
- One study combined bolus cisplatin (CDDP) with infusional 5-fluorouracil (5-FU) and radiation therapy in a phase II trial of the Eastern Cooperative Oncology Group. The regimen resulted in an overall response rate of 95%; however, significant toxicity occurred, indicating that this regimen was near the maximal tolerated dose
- Radiation therapy is associated with gastrointestinal and dermatologic toxicity.

Contraindications

Contraindications

- Known human immunodeficiency virus (HIV) infection is not necessarily a contraindication to standard recommended treatments, and these patients should continue on antiretroviral therapy throughout chemoradiation. However, patients with cytopenias or with frank manifestations of acquired immunodeficiency syndrome may have a decreased ability to tolerate treatment.
- Other relative reasons that might preclude definitive treatment include previous pelvic radiotherapy or surgery and underlying medical, psychiatric, and/or social reasons.

Qualifying Statements

Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Hong TS, Pretz JL, Suh WW, Herman JM, Abdel-Wahab M, Azad N, Blackstock AW, Das P, Goodman KA, Jabbour SK, Jones WE III, Konski AA, Koong AC, Rodriguez-Bigas M, Small W Jr, Thomas CR Jr, Zook J, Expert Panel on Radiation Oncologyâ€“Rectal/Anal Cancer. ACR Appropriateness CriteriaÂ® anal cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2013. 14 p. [56 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1998 (revised 2013)

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

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Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Rectal/Anal Cancer

Composition of Group That Authored the Guideline

Panel Members: Theodore S. Hong, MD (*Principal Author*); Jennifer L. Pretz, MD (*Research Author*); W. Warren Suh, MD (*Panel Chair*); Joseph M. Herman, MD, MSc (*Panel Vice-chair*); May Abdel-Wahab, MD, PhD; Nilofer Azad, MD; A. William Blackstock, MD; Prajnan Das, MD; Karyn A. Goodman, MD; Salma K. Jabbour, MD; William E. Jones, III, MD; Andre A. Konski, MD; Albert C. Koong, MD; Miguel

Rodriguez-Bigas, MD; William Small Jr, MD; Charles R. Thomas Jr, MD; Jennifer Zook, MD

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Poggi MM, Konski AA, Suh WW, Blackstock AW, Herman JM, Hong TS, Rodriguez-Bigas M, Small W Jr, Thomas CR Jr, Venook AP, Zook J, Expert Panel on Radiation Oncology-Rectal/Anal Cancer. ACR Appropriateness Criteria® anal cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2010. 11 p.

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2013 Apr. 1 p. Electronic copies: Available in PDF from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available in PDF from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available in PDF from the ACR Web site.
- ACR Appropriateness Criteria® anal cancer. Evidence table. Reston (VA): American College of Radiology; 2013. 23 p. Electronic copies: Available from the ACR Web site.

Patient Resources

None available

NGC Status

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